PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003465	08.10.2004	09.10.2003

International Patent Classification (IPC) or both national classification and IPC
A61K9/72, A61K31/67, A61K31/00

Applicant
JAGOTEC AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/003465

Box No. I Basis of the opinion

1. With regard to the **language,** this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-28
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-28

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I.

1) Although claims 1 and 20, directed to a product claim, have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter, namely a composition, and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, to determine the matter for which protection is sought, and **places an undue burden** on others seeking to establish the extent of the protection.

Hence, claims 1 and 20 do not meet the requirements of Article 6 PCT.

In order to overcome this objection, it would appear appropriate to file an amended set of claims defining the relevant subject-matter in terms of a single claim in each category followed by dependent claims covering features which are merely optional (Rule 6.4 PCT). Applicant should take care however not to add subject-matter which extends beyond the content of the application (Art. 19/34 PCT).

Failure to do so or to give convincing argumentations might lead to the substantive examination of only the first independent claim and its appending claims, and to the raise of a non-unity objection as the common concept between the compositions of claims 1 and 20 is not novel nor inventive over prior art.

2) The wordings in claims 3-6,23-25 and 26 such as "wherein the formulation is capable [...] to provide [...] a variance of no more than +/- 25%" or "wherein the formulation is capable [...] to provide [...] a fine particle fraction of 30 to 70%" or "wherein the formulation is capable of delivering a dosage of [...]" or "wherein mean delivered dose [...] is no more than +/-15% of the dosage contained stated in the label" do not delimit the scope of the protection to be sought and are rather to be construed as an attempt to define the invention by a **result to be achieved,** in particular they only amount to claiming the underlying technical problem.

Such definitions are only allowable under the conditions elaborated in the Guidelines C-III, 4.7. In this instance, however, **such wordings are not allowable because it appears possible to define the subject-matter in more concrete terms, viz. in terms of how the effect is to be achieved by incorporating for example the type and amount of excipients used,,...**

Furthermore it should be noted that these wordings claim a very broad and non-restricting range. It seems indeed that any MDI formulation will fulfil these specifications.

Hence applicant's attention is drawn with the fact such formulations in 3-6,23-25 and 27 **are not recognized as a technical feature** that can confer novelty to the application, **but as a result to be achieved and therefore would be ignored**.

Re Item V.

3) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D6; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, the cited passages of each document in the ISR will be considered.

D1 : WO 03/074024 A (CHIESI FARMACEUTICI S.P.A; DAVIES, REBECCA, JAINE; GANDERTON, DAVID; L) 12 September 2003 (2003-09-12)

D2 : US 2002/018753 A1 (BLONDINO FRANK E ET AL) 14 February 2002 (2002-02-14)

D3 : US 6 054 488 A (OLIVER ET AL) 25 April 2000 (2000-04-25)

D4 : WO 00/48587 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; CLARK) 24 August 2000 (2000-08-24)

D5 : US 6 475 467 B1 (KELLER MANFRED ET AL) 5 November 2002 (2002-11-05)

D6: US5709884

4) Novelty and inventive step

4a) The subject-matter of claim 20, directed to formoterol MDI formulation wherein the

moisture content is in the range of from 50-800 ppm, does not meet the criteria of Article 33(1) PCT, because it is not new over D1-D6, in particular D1-D2, in the sense of Article 33(2) PCT .

The subject-matter of independent claim 1 and its dependent claims 2-19,24-28 is not novel in the light of D1-D6, in particular D3, D5, because the prior art documents describe an aerosol formulation for MDI, comprising formoterol in suspension, a HFA propellant and ethanol.
Furthermore these documents point out the **chemical instability of formoterol due to moisture or high water content** (see for example D1: p.14 L.18-26, p.16 L.24-27, p.19 L.19-24, Examples 3-4; D2: Tables 2-3; D5: col.3 L.33-45, col.9 L.46-47).
Besides D6 discloses a process for providing a stable crystallinic form of formoterol, wherein the **formoterol particles are dried** (see col.2 L.56-col.3 L.9, Example 3).
Therefore in order to avoid instability problem, it is **implicit and obvious** that the formoterol particles which were used in prior art document fulfil **the water content specification** as described in present application.

It could be argued that the prior art does not provide exactly and in a convincing manner that formoterol has a water content of 4.8-4.28% by weight. Nevertheless, the formoterol formulations of D1-D6 show a good stability, that is to say the formoterol which were used would **implicitly fulfill the water content specification** as described in present application.

In such a case an objection as to lack of novelty arises in the first place and **the burden is on the Applicant to provide evidence** for the novelty of the claimed composition. Such evidence should be of a technical character (for instance data comparing conventional and dried formoterol). The mere statement that the formoterol of prior art does not have the same water content such as described in present application is not sufficient (see also guidelines **C-IV, 7.5., implicit parameter**).

4b) If the applicant was able to show, e.g. by **appropriate comparative tests**, that differences do exist with respect to the parameter "water content in formoterol particles", the said claims would lack the necessary inventive because the applicant

does not show that the **present "water content range" in formoterol** is the **only feature per se**, that is to say without the influence of other stabilizing parameters, which would permit to stabilize formoterol in a MDI formulation containing a propellant and ethanol.

With respect to other stabilizing parameters, applicant's attention is drawn to the teachings of prior art D1-D6.
For example D1 teaches the setting of an optimal pH value and water amount (see p.16 L.10-26), p.19 L.19-24, Examples 3-4, Figure 2).
D3 prones the use of small amount of ethanol, of oleic acid and/or of a bulking agent (see col.2 L.20-23, col.3 L.5-42, col. 4 L.7-14, col.6 L.49-67, Ex.26-33).
D5 recommends the use of a cromone in order to suppress the disadvantageous effect of water on the stability and dispersion of active substances (see col.3 L.33-52, col.4 L.51-65, Examples 1,6,11,12 etc...).

In the absence of valid comparative tests wherein the influence of other stabilizing parameters are avoided (i.e. the **only distinguishing feature** between the present and comparative formulations **is** the water content in formoterol), inventive step cannot be acknowledged because the problem is not solved by the feature "specific water content range", but rather by other parameters such as a the use of a surfactant, the use of a cromone, the setting of a specific pH value etc....

4c) Should the applicant renders the subject-matter of independent claim 1 novel by introducing into the claims the use of a **specific excipient or a specific range or a specific process** or whatever, inventive step would be recognized **only if he demonstrates** that the **introduced** technical feature provides **a surprising or synergetic effect** that the skilled man in the art could not deduct from the prior art.

In the absence of a surprising effect, inventive step cannot be acknowledged because the introduced technical feature would be considered as an **obvious alternative** that the skilled man in the art would perform **routinely** in order not to interact with prior art.

4d) Any information the applicant may wish to submit concerning the subject-matter of

the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

Re Item VII.

5) Contrary to the requirements of Rule 5.1(a)(ii) PCT, it seems that the relevant background art disclosed in the documents D1-D2, D4 and D6 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII.

6) Present application does not fulfil the requirement of Art.6 PCT for lack of clarity because too many independent claims of the same category have been filed (see herein §1).

7) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter **which extends beyond the content of the application as filed**.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

8) The applicant is kindly requested to take account of the above objections and **give convincing argumentations**. In particular the applicant is requested to provide valid comparative **stability** tests, wherein the **only** distinguishing parameter is the **water content** of the conventional and dried formoterol.